IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Siegfried ANSORGE et al. Examiner: SIMMONS, CHRIS E

Serial No.: 10/584,072 Group Art Unit: 1612

Filed: APRIL 3, 2007 Confirmation No.: 6887

Title: **USE OF AT LEAST ONE EFFECTOR OF GLUTATHIONE METABOLISM TOGETHER WITH ALPHA-LIPOIC ACID FOR THE TREATMENT OF CHRONICALLY OBSTRUCTIVE LUNG DISEASES**

PRE-APPEAL BRIEF REQUEST FOR REVIEW

MAIL STOP: AFTER FINAL
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants request review of the Final rejection in the above-identified application. No amendments are being filed with this request. This request is being filed with a notice of appeal. No more than five (5) pages are included in the request. The review is requested for the following reasons.

The Office Action mailed December 24, 2008 alleges that the instantly claimed method(s) are unpatentable over Biewenga et al. (*ABB*, 1994), Mira et al. (*Biochem. Pharmacol.*, 1994) further in view of Yeadon (US publication No. 2004-0167153; *hereinafter* the '153 publication). The Office Action mailed June 11, 2009 sustains this rejection. The basis for this rejection is that Biewenga's disclosure on the usefulness of α-lipoic acid against lung emphysema in combination with Mira's disclosure of the use of silibinin as an antioxidant and HOCl scavenger, *prima facie* renders obvious the claims of the instant application. The Office Action cites *In re Kerkhoven* 205 USPQ 1069 (CCPA 1980) to assert that "The combination of compounds for a certain function where the compounds are known to have the function individually is *prima facie* obvious." At the outset, Appellants submit that this statement is incorrect. In *Kerkhoven*, the CAFC held that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose (emphasis added)." In view of the Examiner's misplaced reliance on *In re Kerkhoven*, the *prima facie* obviousness rejection is thus without merit.

Unexpected effects

In applying *Kerkhoven*, the Office Action asserts that "there is no evidence in the record establishing the Appellant's combination of agents is any more effective or in any way different than any single member of the combination." This statement is incorrect. The instant specification explicitly teaches to a skilled worker that the claimed invention involves much more than mere mixing of the two compounds and that the claimed combination leads to "unexpected results." To this end, the Board is cordially requested to review the disclosure contained in Tables 6 and 7 and the analysis thereof provided in Examples 4 and 5.

For example, in Example 4 of the instant specification, an unexpected effect of a combination of α-lipoic acid and silibilin on the cellular thiol status of alveolar macrophages is disclosed. It is taught therein that "With the addition of the monosubstances α-lipoic acid or silibinin, no modulation of the cellular thiol expression was to be observed. In contrast, with the combination of α-lipoic acid and silibinin, a clear rise in cellular thiol expression could be demonstrated, starting after 24 hours, which reached a superadditive and significant maximum over the entire test period in the presence of 70 µg/ml silibinin. (emphasis added)." Similarly, in the *ex vivo* phagocytosis assay (e.g., Example 5), it was demonstrated that "the induction of phagocytosis with the combination of α-lipoic acid and silibinin in a concentration of 70 µg/ml was similar [to the one afforded by a combination of α-lipoic and ambroxol]. Here, too, a significant improvement in the capacity for phagocytosis was demonstrated, parallel to a restoration of the thiol status (emphasis added)." Thus it is clear from the experimental evidence disclosed in the instant application that the claimed molecules(s) display unexpected advantages over the totality of the disclosure contained in the cited references.

As evidenced from the Examiner's remarks in the final action mailed June 11, 2009, the evidence of unexpected properties of the claimed combination has not been considered on its merits. The Office Action now alleges that there is no side by side comparison of the closest art. This contention is simply incorrect. Based on the Examiner's rejection, the closest prior art is the combined teachings by Biewenga and Mira, which, at most, teach the properties of α-lipoic acid or silibinin in singularity. Example 4 of the present specification provides a side-by-side comparison of the agents when used singularly and in combination. In particular, the disclosure therein evaluates the effects of "monosubstances" (i.e., α-lipoic acid or silibinin) *versus* the claimed combination with respect to elevation of intracellular thiol status in COPD cells. The experimental evidence provided therein explicitly teaches that the claimed combination yields an unexpected (e.g., superadditive) effect. Furthermore, the claimed combination's effects on *in vitro* thiol status were found to correlate

with the *in vivo* activity (shown in Example 5). Thus, although not required, the experimental evidence clearly establishes unexpected properties of the claimed combination in the *in vitro* as well as *in vivo* setting. It would clearly be disingenuous for the PTO to sustain this rejection in view of the totality of the evidence provided by the present disclosure.

The Examiner further questions the validity of the control experiments (i.e., results of experiments performed with 70 μg of silibinin or 10 μg of lipoic acid). The Examiner's position is that "proper showing of unexpected results would include a comparison to 80 μg of lipoic acid alone and 80 μg of silibinin alone." This contention is without merit because there is no requirement that the exact same doses of α-lipoic acid and silibilin be used in the comparative assessment. All is required is that the amounts of the respective agents in the combination be identical to that which is used in singularity. Such has been established by the present disclosure. For example, as shown in Table 6, the intracellular thiol concentration in COPD cells at 24 hours was 61.6% ±13.9% of normal cells. When the same COPD cells were treated with 10 μg of α-lipoic acid or 70 μg of silibilin, the intracellular thiol status was almost unchanged (60.3% ±21% with α-lipoic acid and 56.1% ±12.4% with silibilin). However, with a combination of 10 μg α-lipoic acid and 70 μg of silibilin, the intracellular thiol status was elevated up to and beyond normal levels (102.5% ± 22.6%). Similar observations were reported in the *in vivo* phagocytosis assay, the results of which are provided in Table 7. As such, the PTO's contentions are scientifically baseless.

The Office Action mailed June 11, 2009 further alleges that "the claims are not commensurate in scope to any example in Tables 6 or 7." This contention is respectfully traversed. Insofar as the objective indicia of unobviousness for the claimed combination has been established by the way of experimental evidence, and the Examiner has failed to provide any reasons as to why one of ordinary skill would doubt that doses that are different from the exemplified doses would cease to yield the demonstrated pharmacological effects, the PTO's contentions are without merit. The data provided by the present specification are more than adequate. See *In re Saunders*, 444 F.2d 599, 170 USPQ 213 (CCPA 1971).

No *prima facie* case

Appellant respectfully submits that the PTO has not established that the claimed methods are rendered *prima facie* obvious by the disclosure in the aforementioned references. To this end, the decision in *Kerkhoven* was made with respect to spray-dried detergent compositions comprising two detergents, one anionic and the other nonionic detergent materials, whereas the agents used here have different biological targets and, as such, effects. Contrary to the PTO's assertion, the compounds of each reference are not taught for the same specific purpose. Clearly, the

pharmacology of the two agents is different, as are the disclosed uses. The cited teachings of the Biewenga and Mira, even at the broadest interpretation, do not teach or suggest the combined use of the two molecules in the manner recited in the instant claims. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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